***Title*: Investigation Gone Viral: Application of the Social Mediasphere in Research**

***Short Title*:** Research Gone Viral

***Authors*:** Craig Lammert, MD[1]; Megan Comerford[1]; Joshua Love[1], James Robert Bailey, MD[2]

Indiana University School of Medicine, [1] Department of Digestive and Liver Disease, [2] Department of Internal Medicine.

***Grant Support*:** This publication was made possible with support provided to Craig Lammert from Grant Numbers, KL2TR001106, and UL1TR001108 (A. Shekhar, PI) from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award.

***Abbreviations*: AHRN:** Autoimmune Hepatitis Research Network; **AIH:** Autoimmune Hepatitis; **AIHA:** Autoimmune Hepatitis Association; **IRB:** Institutional Review Board; **Mturk:** Mechanical Turk; **PB:** plastic bronchitis; **PLE:** protein losing enteropathy; **RDCRN:** Rare Disease Clinical Research Network; **SNS**: Social Networking Sites

Acknowledgements: The authors wish to extend their gratitude to Drs. Farris Timimi (Mayo Clinic – Rochester) and Naga Chalasani (Indiana University) for their helpful suggestions and commentary.

***Correspondence*:** Craig Lammert, MD
702 Rotary Circle, Suite 205
Indianapolis, IN 46202
Email: clammert@iu.edu
Phone: 317-278-1637
Fax: 317-278-6780

***Disclosures*:** Craig Lammert, MD: Author has nothing to disclose

Megan Comerford: Author has nothing to disclose

Josh Love: Author has nothing to disclose

Robert James Bailey, MD: Author has nothing to disclose

***Author Contributions*:** Craig Lammert, MD: Manuscript conception development, composition

Megan Comerford: Manuscript development, composition

Josh Love: Manuscript development, composition

Robert James Bailey, MD: Manuscript development, literature review

Keywords: Autoimmune hepatitis, social media, Facebook

The research paradigm in the United States remains burdened by numerous obstacles impeding the progress of scientific investigation.[1] Barriers to effective and efficient conduct of academic research include growing costs, delayed results, adequate staffing, and regulatory encumbrances.[2–5] Beyond these system constraints, patient recruitment in research studies can be time-intensive, costly, and limited by minimal participant diversity.[6,7] The social mediasphere, an intertwining universe of online social media applications, may represent a new model in research methodology that will bridge current research challenges in all medical fields. Investigators and study staff will require a fundamental appreciation of social media structure, existing methodology, and advantages and limitations in order to effectively conduct research with this novel strategy.

The internet is a ubiquitous, continual stream of information to those with means of access. Much of humanity has accepted and now expects readily accessible knowledge and rapid communication. A need for online connectedness drove cyberspace innovation, resulting in the establishment of social networking sites (SNS) such as Facebook, Twitter, Instagram, YouTube and LinkedIn. These public websites have provided the foundations of digital communities in which users construct personal profiles, create and share user-generated media, and interact with other users virtually.[8,9] Global membership within SNS has increased tremendously since their incarnation. As of September 2014, 74% of online adults in the United States use SNS and over half report routine use of 2 or more separate services.[10] Facebook (www.facebook.com), the largest SNS at over 1.3 billion users worldwide, provides a media platform that consumes 40 minutes of the average American user's day.[10,11] SNS have quickly become a communication fixture between family and friends for sharing electronic posts, pictures, and videos. However, their spectrum of use has grown, now including vast networks of information providing users a portal to pursue specific questions about individual health, obtain medical information about disease conditions[12], and participate in active health-related support

groups.[13] Considering the number of individuals engaged in this media, the research community has been slow to recognize the potential of this resource for conducting research and recruiting proactive study participants.

Prior to the digital age, individuals seeking similar health information commonly gathered together in physical support networks. However, the advent of SNS has simplified formation of these groups, providing online communities where e-patients and e-caregivers can successfully support one another with the provision of information, resources, and outcomes at any time without geographic limitations. Distinct *group pages* (i.e., public or private) on Facebook can be created or identified and joined by users, thus opening communication channels to receive and distribute opinions for group-generated questions and commentary. Gastroenterology-related disease groups are now well represented on Facebook, often including multiple distinct pages for both common and rare disorders (Table 1). This social support shift has evolved with societal interests, as many patients find it easier to communicate online with strangers rather than speak with family directly.[14]

Application of SNS in research conduct and collection is likely to be the most impactful within the study of rare diseases. According to the National Institutes of Health, these disorders have a prevalence of less than 200,000 persons in the US. Despite perceived scarcity, there are approximately 7,000 known rare disorders affecting up to 25 million people (7% of population) in the US alone.[15] Disease underpinnings, optimal treatment, and expected outcomes of rare diseases are commonly limited to studies with minimal patient enrollment due to low prevalence and population distribution. In 2003, the National Center for Advancing Translational Sciences led an initiative to develop the Rare Disease Clinical Research Network (RDCRN) in order to overcome well-defined obstacles in rare disease research. The RDCRN, composed of 22 clinical research consortia, has sought to establish study cohorts and collect data on more than 200 rare diseases. Despite published successes of the RDCRN in forming dedicated research

consortia for specific disorders, a majority of recognized rare diseases remain without national initiatives or study incentives to fuel proactive and novel investigation.

SNS enable investigators to quickly establish disease specific cohorts and disseminate research opportunities across geographic barriers in short times with low costs (Table 2). An example of SNS implementation in rare disease research is highlighted in a study of Fontan-associated protein losing enteropathy (PLE) and plastic bronchitis (PB).[16] Investigators provided a single recruitment post on two existing patient-run and disease-specific Facebook groups, directing interested participants to either a study-specific Facebook group or publically-available website that served as a study material repository. The single study recruitment post generated respondent-driven study participation for one year, propelled by member discussion and reposts. This simple methodology generated the largest contemporary survey cohort of Fontan associated PLE and PB patients ever reported (671 respondents) at no cost. Furthermore, sole utilization of SNS to recruit, disseminate, and collect epidemiologic observations has been successfully employed by other rare diseases including neuroendocrine cervical carcinoma among others. For example, Zaid et al.[21] used Facebook to complete cross-sectional epidemiologic and quality of life survey data among patients with neuroendocrine carcinoma of the cervix. Fifty-seven women across 8 countries and 4 continents completed an 81 question study instrument in a single month, thus solidifying the feasibility of SNS to collect patient response data.

Overall growth in US funding for medical research has slowed to 0.8% per year between 2004 and 2012; therefore, innovative approaches to reduce research expenses without impacting study design or time are paramount.[17] Outside SNS specific groups, investigator-purchased study advertisements on SNS can effectively target users based on a number of inclusion criteria such as age, gender, geographic location, and even specific SNS group memberships. Study-specific ads, configured and distributed through SNS, can be displayed

directly on a user's Facebook portal or content feed. Selecting or "clicking" on an ad can provide means for an interested patient to participate. This approach existed as a minor adjunct to physical study recruitment until 2013, when Kapp et al. employed Facebook advertisement as an exclusive study recruitment mechanism.[18] In 11 days, 3 separate study ads on mammography were displayed for 374,225 women between the age of 35 and 49 with a total study cost of $300.

Twitter (www.twitter.com), another popular SNS that allows registered users to communicate with others using short messages, has also proved to be a powerful tool to distribute epidemiologic surveys. Web services such as Qualtrics, REDCap, and SurveyMonkey can be used to design and collect survey responses via posted survey-linked web addresses. Twitter was recently employed in the development of a cross-sectional survey examining the pregnancy experiences of mothers of advanced maternal age.[19] Investigators *tweeted* (posted on their Twitter account) a web-based questionnaire accessible via a link to national organizations that were thought to have an interest in patient-related research. Recruited participants were then asked to *retweet* (post the study link to be shared with their network of followers) creating a modernized snowball sampling technique. Study participation was not driven by monetary reward and no mention of payment was included in the study advertisements or given at study conclusion. In less than 3 months, 529 mothers were recruited from 359 investigator tweets and subsequent retweets from study participants. This not only highlights social media's effectiveness in study recruitment, but also demonstrates the participants' willingness to contribute to web-based research studies with no compensation.

SNS may also represent a viable mechanism to recruit populations that have been historically challenging to engage with the traditional research model including those with perceived stigma related to disease and even research collaborators. The anonymity associated with this methodology has been appealing to many research subjects, particularly evident in

studies relating to sexual health. Adolescents participating in a web-based survey of sexual health and behaviors reported they were more comfortable providing honest responses using this approach.[20] Furthermore, Khatri et al.[21] recently used SNS to facilitate collaborator recruitment to a large United Kingdom investigator-led study to determine the safety profile of non-steroidal anti-inflammatory drugs following gastrointestinal surgery. The approach included a dedicated YouTube study video, Facebook page, and Twitter feed, ultimately capturing an additional 96 collaborators beyond the 431 recruited via traditional means (webpage, email, and word of mouth).

Successful implementation of SNS and web-based tools in the conduct of research is rooted in a fundamental understanding of social media applications. This includes developing established relationships with study group moderators and stakeholders, conducting open communication with the local institutional review board (IRB), and constructing different professional and personal SNS accounts. Gaps in SNS expertise among professional clinicians likely remains prevalent as social media utilization in this group ranges between 13% and 47%.[22] Familiarity with common social media platforms such as Facebook and Twitter, as well as their terminology, is important for creating and maintaining a social media presence conducive to web-based research.

Despite the overwhelming advantages of SNS in study conduct, it shares a few similar limitations and biases present in traditional research methods (Table 2). Uncertainty of external validity remains a challenge, as research subjects within SNS studies have historically been younger, healthier, and more educated. However, trends in social media use in 2014 have revealed a shift in these demographics as populations age and internet technology becomes cheaper and more user-friendly. In fact, Facebook is used by over half of individuals sixty-five years and older and is more prevalent in households with incomes less than $30,000/year compared to all other income brackets.[23] However, possible limitations include potential self-

selection bias which may impact subject choice to participate, and difficulty in validation of reported diseases and outcomes represents since maintenance of participant anonymity with this approach often precludes verification of medical records to authenticate responses.[16] Provided that little or no incentive is offered for the completion of social media based studies, there is presumably minimal motivation to intentionally provide false information. Ethical concerns such as recruiting and consenting adolescents are areas in which social media needs further definition when submitting studies to the IRB.[24,25] Privacy concerns are rooted in the maintenance of anonymity of participants, yet investigators may successfully address these concerns by only using SNS as a means to reach patients.

Application of SNS in Autoimmune Hepatitis Research at Indiana University

The study of autoimmune hepatitis (AIH), similar to other rare diseases, continues to be burdened by low study numbers, limited investigators, and proactive patients residing long distances from institutions with ongoing research opportunities. In 2014, we developed the Autoimmune Hepatitis Research Network (AHRN) group page on Facebook (www.facebook.com/groups/autoimmunehep). The AHRN, championed by 6 other collaborating AIH patient groups on Facebook, aimed to fill academic gaps observed in the AIH online support group community. This private group, led by a physician moderator, currently consists of 897 members and is aimed to provide current AIH literature review and commentary, member and study team interactions, and opportunities to participate in AIH research studies at Indiana University. As a private group, members require online verification to join and interact in the community. AHRN group requests are met with close review of member profiles to ensure no signs of member illegitimacy such as no recent personal posts, membership in many large groups, and recent Facebook enrollment.

Our approach to electronic patient recruitment from the AHRN for AIH research questions is shown in Figure 1. Ongoing AHRN studies include both (A) opportunities to

complete disease-specific electronic questionnaires in real time and (B) enrollment into a linked genetic and epidemiologic AIH biorepository at Indiana University. Electronic questionnaire distribution is completed with a web-based survey link posted on the AHRN home page as well as collaborating AIH Facebook groups on weekly intervals throughout a defined study period (Figure 1, A). Study summary statements are provided to interested participants prior to survey initiation, and the decision to complete the posted survey is dependent on the participant review of both inclusion and exclusion criteria. We have six completed or currently ongoing epidemiologic surveys directed at examination of AIH and associated environmental factors, pregnancies, family history, dietary exposures, sleep disturbances, and complementary and alternative medicine practices since AHRN launch. A recent AHRN nutrition and diet survey was electronically distributed weekly for a 30-day period and resulted in 430 (cases: n=152, controls: n=278) completed surveys (75% completion rate). Amazon's Mechanical Turk (Mturk) (www.mturk.com) was used to screen and recruit healthy study controls. Mturk is a website where individuals, meeting specified qualifications, are given small monetary rewards to perform tasks, such as epidemiologic surveys. Study results revealed AIH cases (49%) were less likely to report a history of being breastfed as an infant compared to controls (65%, P = 0.01), and the association remained after adjusting for age and gender (OR: 0.66, P = 0.08).[26] This study was completed at a cost of approximately $0.25 per study participant.

The AHRN has also posted recruitment invitation for inclusion in a national cohort of well-defined AIH patients (Figure 1, B). Study ads posted at monthly intervals on the AHRN Facebook page have successfully recruited 23 patients in 6 months. Study consent via phone conference with our study coordinator also includes the collection of a patient health information request sheet to allow validation of AIH diagnosis by medical record review. This approach has enabled successful collection of 20 saliva-based DNA kits and epidemiologic survey tools to date. Distant study recruitment with this technique provides challenges such as establishment of

trusting patient-investigator relationships and eventual collection of local medical records to verify study criteria. Our experience has shown online rapport is built over time, and patient skepticism can be minimized with study transparency and participant feedback. Furthermore, data collection remains institution-specific, and eventual release of medical information requires the correct request forms and persistency.

These close research interactions between the study team and active online patients have led to collaborative growth in the past 2 years, resulting in the formation of an international physical support group called the Autoimmune Hepatitis Association (AIHA) (https://www.facebook.com/autoimmunehepatitisassociation). Supporting Indiana University physicians and online patient leaders constructed the first national meeting of the AIHA in May 2015, allowing 122 patients and caregivers to convene for a 2-day conference with multiple patient-centered didactics as well as opportunity to enroll in the Indiana University AIH biorepository.

We believe SNS provide investigators with a powerful new tool to overcome limitations of traditional research methods. With the number of people connected to various SNS, geographical barriers are eroded while researchers are able to reach orphan diseases deemed inaccessible in the past. Furthermore, study costs accrued are negligible while study recruitment and data collection are expeditious. Our own experience and review of prior studies provide the recognition of an immense research potential with the understanding of study design, advantages and limitations, and pragmatic approaches unique to this innovative methodology. Utilization of SNS to conduct research presents a viable alternative to traditional research methods with the capability to supplement the areas that have historically been deficient.

References

1. Sung NS, Crowley WF, Genel M, et al. Central challenges facing the national clinical research enterprise. J. Am. Med. Assoc. 2003;289:1278–1287.

2. Campbell EG, Weissman JS, Moy E, et al. Status of clinical research in academic health centers: Views from the research leadership. J. Am. Med. Assoc. 2001;286:800–806.

3. Oinonen MJ, Crowley Jr WF, Moskowitz J, et al. How do academic health centers value and encourage clinical research? Acad. Med. 2001;76:700–706.

4. Frist WH. Federal funding for biomedical research: Commitment and benefits. J. Am. Med. Assoc. 2002;287:1722–1724.

5. Anon. Developing the Clinical Investigator Workforce: Clinical research roundtable symposium I. In: Washington D.C.: National Academy Press; 2001.

6. Lovato LC, Hill K, Hertert S, et al. Recruitment for controlled clinical trials: Literature summary and annotated bibliography. Control. Clin. Trials 1997;18:328–352.

7. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. J. Am. Med. Assoc. 2001;286:708–713.

8. boyd danah m., Ellison NB. Social Network Sites: Definition, History, and Scholarship. J. Comput.-Mediat. Commun. 2007;13:210–230.

9. Grajales III FJ, Sheps S, Ho K, et al. Social Media: A Review and Tutorial of Applications in Medicine and Health Care. J. Med. Internet Res. 2014;16:e13.

10. Duggan M, Ellison NB, Lampe C, et al. Social Media Update 2014. Pew Res. Cent. Internet Am. Life Proj. Available at: http://www.pewinternet.org/2015/01/09/social-media-update-2014/ [Accessed February 2, 2015].

11. Anon. Americans Now Spend More Time on Facebook Than They Do on Their Pets. BloombergView. Available at: http://www.bloomberg.com/bw/articles/2014-07-23/heres-how-much-time-people-spend-on-facebook-daily [Accessed March 6, 2015].

12. Cline RJ, Haynes KM. Consumer health information seeking on the Internet: the state of the art. Health Educ. Res. 2001;16:671–692.

13. Bender JL, Jimenez-Marroquin M-C, Jadad AR. Seeking support on facebook: a content analysis of breast cancer groups. J. Med. Internet Res. 2011;13:e16.

14. Jones R, Sharkey S, Smithson J, et al. Using metrics to describe the participative stances of members within discussion forums. J. Med. Internet Res. 2011;13:e3.

15. Anon. About ORDR | Office of Rare Diseases Research (ORDR-NCATS). Available at: https://rarediseases.info.nih.gov/about-ordr/pages/30/about-ordr [Accessed July 7, 2015].

16. Schumacher KR, Stringer KA, Donohue JE, et al. Social Media Methods for Studying Rare Diseases. PEDIATRICS 2014;133:e1345–e1353.

17. Moses H, Matheson DHM, Cairns-Smith S, et al. The Anatomy of Medical Research: US and International Comparisons. JAMA 2015;313:174.

18. Kapp JM, Peters C, Oliver DP. Research Recruitment Using Facebook Advertising: Big Potential, Big Challenges. J. Cancer Educ. 2013;28:134–137.

19. O'Connor A, Jackson L, Goldsmith L, et al. Can I get a retweet please? Health research recruitment and the Twittersphere. J. Adv. Nurs. 2014;70:599–609.

20. Nicholas A, Bailey JV, Stevenson F, et al. The Sexunzipped Trial: Young People's Views of Participating in an Online Randomized Controlled Trial. J. Med. Internet Res. 2013;15:e276.

21. Khatri C, Chapman SJ, Glasbey J, et al. Social media and internet driven study recruitment: evaluating a new model for promoting collaborator engagement and participation. PloS One 2015;10:e0118899.

22. Muhlen M von, Ohno-Machado L. Reviewing social media use by clinicians. J. Am. Med. Inform. Assoc. JAMIA 2012;19:777–781.

23. Social Networking Fact Sheet. Pew Res. Cent. Internet Sci. Tech. Available at: http://www.pewinternet.org/fact-sheets/social-networking-fact-sheet/ [Accessed July 7, 2015].

24. Amon KL, Campbell AJ, Hawke C, et al. Facebook as a Recruitment Tool for Adolescent Health Research: A Systematic Review. Acad. Pediatr. 2014;14:439–447.

25. Close S, Smaldone A, Fennoy I, et al. Using Information Technology and Social Networking for Recruitment of Research Participants: Experience From an Exploratory Study of Pediatric Klinefelter Syndrome. J. Med. Internet Res. 2013;15:e48.

26. Comerford M, Marri S, Chalasani N, et al. A Preliminary Study Utilizing Social Media and Crowd-sourcing Shows an Inverse Relationship Between Breast Feeding as an Infant and the Presence of Autoimmune Hepatitis. Hepatology 2014;60:214A.

Table 1: The Spectrum of Gastroenterology-related Diseases with Active Private Groups on Facebook

Specific Gastroenterology-Related Diseases	Number of Private Groups on Facebook	Range of Members per Group	Mean Number of Members per Group
Eosinophilic Esophagitis	5	113-3,923	1,197
Barrett's Esophagus	1	431	431
Celiac Disease	13	510-9,860	2,503
Crohn's Disease and Ulcerative Colitis	27	2154-20,169	5,752
Non-Alcoholic Fatty Liver Disease	4	504-3,895	1,633
Primary Biliary Cirrhosis	3	391-2,567	3,682
Primary Sclerosing Cholangitis	4	872-2,773	1,911
Autoimmune Hepatitis	7	188-1,377	620

Table 2: Advantages and Disadvantages of SNS in Research Methodology

Advantages	Disadvantages
• Minimizes social stigma attached to disease or minority status. • Cost is contained via reduction of staffing needed to recruit, conduct, and follow-up with patients. • Extends recruitment to rural areas and across international borders. • Facilitates exchange of information between researchers and participants. • Alternative contact method for study follow-up. • Data can be collected quickly and study recruitment can occur 24 hours a day. • Development and conduct of study is easy and intuitive. • Collaborator recruitment is feasible via the same approach. • Allows patients to engage research opportunities and maintain a proactive role in disease efforts.	• Historically, populations tend to be younger, more educated, and from higher socioeconomic classes. • Requires baseline knowledge of SNS and linked applications. • Sample and self-selection bias may have impact on external validity. • Recruitment is dependent on patient review of inclusion/exclusion criteria, data is patient-reported. • Local IRBs may be unfamiliar with methodology.

Figure 1: Autoimmune Hepatitis Research Network (AHRN) Approach to Study Recruitment at Indiana University